Am. J. Hum. Genet. 45:487–488, 1989

Invited Editorial: Expression of Lactase during Development

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Intolerance to lactose has been a major concern of gastroenterologists for the past 25 years. Most of the world's adults are lactose intolerant and cannot digest large amounts (>50 g) of lactose (Simoons 1970; Johnson et al. 1974; Flatz 1989). Lactose-intolerant individuals manifest a clinical reaction of abdominal distention, flatus, and often diarrhea. Some individuals, on the other hand, readily digest lactose—for example, children less than 5–7 years of age, the Punjabi of India, and certain tribal groups such as the northern Europeans and the milk-drinking nomads of Arabia and central and west Africa.

The inability to digest lactose appears in most of the world's people in late childhood and adult life. The pathogenesis of the phenomenon is related to the amount of lactose in the diet and to the ability of the intestinal lactase to digest that sugar. In all animals (with the exception of certain species of Pinnipedia [Kretchmer and Sunshine 1967] and the tribal groups mentioned above), the enzyme lactase first appears in late gestation, is most active in the perinatal period, and by the age of full weaning decreases to about 10% of its original level (Blaxter 1961; Doell and Kretchmer 1962; Auricchio et al. 1963; Dahlquist et al. 1963).

There have been many attempts to understand this phenomenon. From a genetic viewpoint (Flatz 1989) the maintenance of the activity throughout life is governed by dominant genetics, whereas the loss of activity has been explained as a recessive condition. Since the changes in enzymatic activity follow a developmental pattern, some researchers (Sahi et al. 1973; Ransome-Kuti and Kretchmer 1975) have suggested a mutation in a regulatory gene, while others (Ho et al. 1982) discuss allelic relationships.

The article by Sebastio et al. (1989) in this issue opens a new mode of thinking for the entity of persistence or nonpersistence of lactase. The biological characteristics of the enzyme are the following:

1. The active molecule is expressed only in the mammalian enterocyte (primarily small intestine). Lactase is formed intracellularly as a large molecule glycosylated with mannose. This molecule is acted on proteolytically intracellularly, and more-complex glycosylation occurs in the Golgi system. The mature enzyme has a molecular weight of about 160,000, and it is placed in the membrane, where it is anchored down by a hydrophobic chain of amino acids and possibly phosphatidylinositol (Skovbjerg et al. 1984; Naim et al. 1987; Semenza and Aurcchio 1989).
2. The enzyme is markedly decreased (10% of the original value) in the enterocytes of all animals in adult life. However, in certain humans the enzyme can be detected in the enterocyte.
3. In particular species of Pinnipedia where lactose does not appear in the maternal milk, there is no lactase present in the enterocyte (Kretchmer and Sunshine 1967). This finding represents an entirely different genetic situation.

Mantei et al. (1988), who are from the same laboratory as Sebastio et al., were able to clone the cDNA for lactase. Sebastio et al. took this information and studied the mRNA for lactase in different situations. Their findings are surprising. The mRNA for lactase is in high concentration in the rabbit enterocyte during the perinatal period and then decreases to low concentrations at weaning. These results were expected, but in the enterocyte from the adult, the mRNA reappeared in an elevated concentration. Sebastio et al. present evidence of elevated mRNA for lactase in humans with persistent lactase. In addition, there is a considerable amount of mRNA in those individuals in whom the lactase is nonpersistent. Similar data have been obtained from another laboratory (Freund et al. 1989). We will have to wait for the full explanation of these findings. Data are needed to explain the depression of translation of the DNA at weaning and the recrudescence later

Received July 25, 1989.

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The contents of this article represent the opinion of the author and have not been peer reviewed.

0002-9297/89/4504-0001$02.00

with the production of mRNA. It is apparent that the explanation lies at the level of transcription or post-transcription. There is evidence (Freund et al. 1989) that a large molecule (molecular weight 350,000) is formed and accumulates in the enterocyte. This molecule cross-reacts with antibodies for lactase. This precursor molecule cannot be found in the membrane.

Although many aspects tying the molecular biology to the biological and genetic findings are still obscure, I believe that the answers are on the horizon and will probably derive from the laboratories in Zurich or Strasbourg. These scientists have the material and capability of making giant steps.

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